UNITED STATES OF AMERICA
BEFORE THE FEDERAL TRADE COMMISSION

In Re: Petition to Clarify Certain Aspects of Health Products Compliance Guidance

Introduction

The Council for Responsible Nutrition (CRN) files this petition to request that the Federal Trade Commission (FTC) clarify, through further guidance or otherwise, certain aspects of its new Health Products Compliance Guidance (Guidance).[1] Specifically, CRN asks that the FTC clarify the following points.

- **There is no bright-line requirement that a company possess randomized, controlled clinical studies before making so-called "health benefit" claims for dietary supplements or food.** Despite statements otherwise in the Guidance, such a bright-line requirement not only lacks any legal basis, but also conflicts with the existing intricate statutory framework Congress has created for dietary supplements and food, versus drug products. Any such bright-line clinical trial requirement, in fact, would even exceed the current standard for drug approval, which while purposefully more rigid than the substantiation standard Congress created for dietary supplement and food claims, still allows for flexibility.
- **There is no requirement for full product testing versus testing of certain ingredients.** Despite the Guidance suggesting otherwise, numerous courts have accepted testing on discrete ingredients, versus a product's full ingredient combination, as adequate claim substantiation for products like dietary supplements and food.
- **Professionals like nutrition researchers, nutritionists, and pharmacologists can be suitable scientific experts to assess claim substantiation for dietary supplements and food.** Breaking with the traditional requirement that a scientific expert opining on claim substantiation merely have "relevant" expertise, the Guidance seeks to impose a requirement that scientific experts have expertise "relevant [to the specific] disease, condition, or function to which the representation relates" – presumably meaning, for instance, that only a cardiologist could opine

[1] The Council for Responsible Nutrition (CRN), founded in 1973 and based in Washington, D.C., is the leading trade association representing dietary supplement and functional food manufacturers, marketers and ingredient suppliers. CRN companies produce a large portion of the functional food ingredients and dietary supplements marketed in the United States and globally. Our member companies manufacture popular national brands as well as the store brands marketed by major supermarkets, drug stores and discount chains. These products also include those marketed through natural food stores and mainstream direct selling companies. CRN represents more than 180 companies that manufacture dietary ingredients, dietary supplements and/or functional foods, or supply services to those suppliers and manufacturers. Our member companies are expected to comply with a host of federal and state regulations governing dietary supplements and food in the areas of manufacturing, marketing, quality control and safety. Our supplier and manufacturer member companies also agree to adhere to additional voluntary guidelines as well as to CRN's Code of Ethics. Learn more about us at www.crnusa.org.

on support for a claim about maintaining a healthy heart. Such a restricted view has no statutory or other legal basis.

- **Dietary supplements and foods are prohibited from making claims to treat or prevent disease without authorization from the Food and Drug Administration (FDA).** Numerous examples appearing in the Guidance convey, erroneously, that as long as claims are adequately substantiated and otherwise non-misleading, disease claims are allowed for dietary supplements and food.

I. Congress Established Flexible Substantiation Standards for Dietary Supplements in Order to Promote Public Health

A. The Substantiation Standard for Drug Claims

To understand the substantiation framework developed by Congress for dietary supplements and food, it is necessary to first examine the drug standard. For new, non-generic drugs to be approved by FDA, they must be supported by "substantial evidence of effectiveness."[2] Such "substantial evidence" is defined by statute as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof."[3] This standard takes into account both the nature of drug claims (*i.e.*, that they are promising a direct effect on disease) and drug safety risks.

In assessing the required studies, the FDA conducts a "benefit-risk assessment," to "ensure that the benefits of the drug outweigh its risks."[4] According to the FDA, that analysis can be challenging, particularly "in cases where the potential for serious safety risks is identified or expected to exist, *e.g.*, risks that are life-threatening or associated with significant morbidity."[5]

With the Dietary Supplement Health and Education Act of 1994 (DSHEA), Congress amended the Food, Drug, and Cosmetic Act (FDCA) to create a clear distinction between drugs and dietary supplements. DSHEA not only exempted dietary supplements from FDA drug approval, but also created a claims regime specifically for dietary supplements.[6] When enacting DSHEA, Congress recognized that the safety of supplements and their health benefits warranted a new regulatory framework to protect consumer access to both the products themselves and accurate information about these products. As part of this framework, DSHEA distinguishes supplements from drugs in several notable ways, including the type of claims permitted for supplements and the type of substantiation needed to support permitted claims.

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[2] FDCA § 505(d) (codified at 21 U.S.C § 355(d)); *see also* 21 U.S.C § 355(c) (addressing approval of non-generic new drugs).

[3] FDCA § 505(d) (codified at 21 U.S.C § 355(d)).

[4] FDA, Benefit-Risk Assessment for New Drug and Biological Products: Draft Guidance, at 4 (Sept. 2021), https://www.fda.gov/media/152544/download; *see also* 21 U.S.C § 355(d); 21 C.F.R. § 314.26.

[5] Benefit-Risk Assessment for New Drug and Biological Products: Draft Guidance, at 4.

[6] Pub. Law No. 103-417, at § 3 (1994), https://ods.od.nih.gov/About/DSHEA_Wording.aspx#sec2.

Supplement marketers are prohibited from making claims that a dietary supplement will "diagnose, mitigate, treat, cure, or prevent disease."[7] Often called "drug" or "disease" claims, such statements will subject the product to regulation as a drug, which requires FDA preapproval for claims and that the claims meet substantiation requirements specific to drug products. As discussed in further detail below, supplement companies can, however, make several types of claims related to a substance's effect on health, as well as claims associating a substance with reduced risk of disease, if they meet specific requirements such as FDA pre-authorization. These types of claims carry substantiation standards distinguishable from the drug standard. Understanding the type of claims permitted for supplements and food, and the substantiation standards under the FDCA, is key to determining appropriate guidance for the evidence needed to support these claims.

In sharp contrast to the drug standard, standards for dietary supplements and food, and their allowed claims have never been as rigid. This flexibility emanates from Congress distinguishing supplement and food claims, versus drug claims, and recognizing that "dietary supplements are safe within a broad range of intake" and have known "benefits in health promotion."[8] Claims permitted for dietary supplements and food generally must meet a "truthful and not misleading" standard, with claims for disease risk reduction requiring FDA authorization under a slightly more specific substantiation standard. Congress reserved the "substantial evidence" discussed above for drug claims that state or imply a product can diagnose, mitigate, treat, cure, or prevent disease. Flexibility is necessary for non-drug claims. The following provides an overview of various claims regimes Congress has created for dietary supplements and food.

B. The Substantiation Standard for Nutritional Support Claims for Dietary Supplements and Food

DSHEA allows, without FDA preapproval, nutritional support claims – specifically, "general well-being" claims, as well as what are known as "structure/function claims," which describe either the "role" or "mechanism by which" a "nutrient or dietary ingredient" affects the body's "structure or function."[9] Structure/function claims encompass claims to support or maintain the body generally – *e.g.*, "Vitamin B12 supports the nervous system" and "Immune support," and claims about certain non-disease cause-and-effect outcomes – *e.g.*, "Promotes weight loss" and "Improves focus."[10] Following passage of DSHEA, FDA explicitly acknowledged that structure/function claims could also be made for "conventional" food, as well as dietary supplements, with the same substantiation standard, disease

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7 21 C.F.R. § 101.93(g)(2); *see also* 21 U.S.C. § 343(r)(6)(C).

8 Pub. Law No. 103-417, at § 2. The safety of supplements nearly 30 years after DSHEA's enactment continues to be well supported. *See e.g.,* CRN Statement, Context is Key to Analyzing Results of New Study on Dietary Supplements in New England Journal of Medicine (Oct. 14, 2015), https://www.crnusa.org/newsroom/context-key-analyzing-results-new-study-dietary-supplements-new-england-journal-medicine. *Contrast* Statement of Comm'r Slaughter Joined by Chair Khan and Comm'r Bedoya Regarding Notice of Penalty Offenses on Substantiation of Product Claims, at 1 (Mar. 31, 2023) (taking inexplicable, contrary position that dietary supplements "can cause serious health problems requiring acute medical attention," based on a single questionable study).

9 Pub. Law No. 103-417, at § 6 (codified at 21 U.S.C. § 343(r)(6)(A)).

10 *See, e.g.*, 65 Fed. Reg. 1000, 1006, 1027-1029 (Jan. 6, 2000).

claim prohibition, and policy considerations as supplements.[11] We use the term "food" to refer to conventional food throughout this submission.

In order to substantiate general well-being and structure/function claims, DSHEA provided that the marketer must possess "substantiation that such statement is truthful and not misleading."[12] With both a prohibition on disease claims and a substantiation requirement that is significantly different from the drug standard, Congress avoided requiring any specific type of research or testing to prove efficacy, and historically, the FTC, the FDA, and the courts have aptly interpreted the substantiation standard in a flexible manner.

Both agencies and the courts have interpreted the DSHEA substantiation standard as a requirement for "competent and reliable scientific evidence" (CARSE), defined flexibly as "tests, analyses, research, studies, or other evidence based on the expertise of professionals in the relevant area, that have been conducted and evaluated in an objective manner by persons qualified to do so, using procedures generally accepted in the profession to yield accurate and reliable results."[13]

The FTC, specifically, has advised for decades that there is "no fixed formula for the number or type of studies required" under the CARSE standard.[14] Rather, the FTC "considers all forms of research."[15] Although "[a]s a general matter," the FTC considers "well-controlled human clinical studies to be the most reliable form of evidence," it "also takes into account other forms of research, including epidemiologic evidence, animal and *in vitro* studies in appropriate circumstances."[16]

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[11] *See, e.g.*, FDA, Distinguishing Liqud Dietary Supplements from Beverages, at 8 (Jan. 2014). Dietary supplements are a type of "food" under the FDCA; therefore, the term "conventional" food is sometimes used to distinguish supplements and what consumers think of as more traditional food products.

[12] Pub. Law No. 103-417, at § 6 (codified at 21 U.S.C. § 343(r)(6)(A)).

[13] *See, e.g.*, FTC, Dietary Supplements: An Advertising Guide for Industry, at 9 (1998); FDA, Substantiation for Dietary Supplement Claims Made Under Section 403(r)(6) of the Federal Food, Drug, and Cosmetic Act, at II.A (2008), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-substantiation-dietary-supplement-claims-made-under-section-403r-6-federal-food.

[14] Dietary Supplements: An Advertising Guide for Industry, at 9; *see also* Substantiation for Dietary Supplement Claims Made Under Section 403(r)(6) of the Federal Food, Drug, and Cosmetic Act, at II.A ("[T]here is no pre-established formula as to how many or what type of studies are needed to substantiate a claim."); FTC Resp. to Rulemaking Petition by Whitaker, *et al.*, Project No. P004501, at 4-8 (Nov. 30, 2000), https://www.ftc.gov/sites/default/files/attachments/press-releases/announced-actions-december-5-2000/001205dietletter.pdf.

[15] FTC Comments in the Matter of Proposed Rule: Regulations on Statements Made for Dietary Supplements Concerning the Effect of the Product on the Structure or Function of the Body, FDA Dkt. No. 98N-0044, at 3 (Aug. 27, 1998), https://www.ftc.gov/sites/default/files/documents/advocacy_documents/ftc-staff-comment-food-and-drug-administration-concerning-dietary-supplements-effect-product/v980023.pdf.

[16] *Id.*

C. The Substantiation Standards for Health Claims and Qualified Health Claims

Several years prior to DSHEA, the Nutrition Labeling and Education Act (NLEA), for the first time, allowed food to be promoted with what are known as "health claims" which "characterize the relationship of [a] nutrient" to disease.[17] DSHEA confirmed that dietary supplements could also make such claims.[18] These claims, which in FDA's view must be about risk reduction rather than any other effect on disease, require the agency's authorization under a standard of "significant scientific agreement."[19] Congress has described that standard as, "by design, more flexible than the standard established by law for FDA to review and approve drugs, which requires demonstration of safety and effectiveness based on 'adequate and well-controlled clinical investigations.'"[20] Congress explained further:

> [T]here is no requirement that health claims be derived from clinical trials, and by its terms, the standard recognizes that scientific agreement on the validity of the claim does not have to be complete. Evidence from a broad range of reliable scientific sources should be considered in determining the adequacy of scientific support. FDA will be expected to take full advantage of the flexibility of the standard to maximize the availability on food and dietary supplement labels and labeling of disease-related information consumers can prudently use to affect their disease risk.[21]

An example of an approved health claim is "Adequate calcium throughout life, as part of a well-balanced diet, may reduce the risk of osteoporosis."[22]

Consistent with Congress's purpose, neither the FDA nor the courts have ever imposed rigid, drug-like standards for what might constitute significant scientific agreement for the purposes of health claims. In guidance on the significant scientific agreement standard, the FDA, in fact, describes how it "focus[es] its review" of health claims "primarily on articles reporting" not only "human intervention" studies but also "observational studies" because both types of research "can provide evidence from which scientific conclusions can be drawn about the substance/disease relationship in humans."[23]

Several years after passage of the NLEA, a line of First Amendment cases held that even if a statement fails to meet the significant scientific agreement standard applicable to health claims, the FDA must still consider whether a "qualified health claim" might be permissible where there is at least "credible evidence" in support of the claim and disclosures might be used to cure any potential deception.[24] The

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17 *See* Pub. Law No. 101-535, at § 2 (1990) (codified at 21 U.S.C. § 343(r)(1)(B)).

18 Pub. Law No. 103-417, at § 13.

19 21 C.F.R. § 101.14(c).

20 S. Rep. 103-410, at § 4 (1994).

21 *Id*.

22 21 C.F.R. § 101.72.

23 FDA, Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims (Jan. 2009), at III.B https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-evidence-based-review-system-scientific-evaluation-health-claims.

24 *See, e.g.*, *Pearson v. Shalala*, 164 F.3d 650, 655, 659-660 (D.C. Cir. 1999); *Pearson v. Shalala*, 130 F. Supp. 2d. 105, 114 D.D.C. (2001); *Whitaker v. Thompson*, 248 F. Supp. 2d 1, 10-11 (D.D.C. 2002)

following is an example of an FDA-approved qualified health claim: "Limited scientific evidence shows that by consuming 500 mg each day of cranberry dietary supplement, healthy women who have had a urinary tract infection (UTI) may reduce their risk of recurrent UTI."[25]

II. Multitudes of Foundational Nutrient Benefits Have Been Established by Research Other than Randomized, Controlled Clinical Testing

The flexibility that Congress has deliberately built into the regulatory regimes governing dietary supplement and food claims makes eminent sense where establishing a connection between a nutrient and healthy function of the body has routinely required not randomized, controlled clinical studies, but the accumulation of evidence from a variety of sources including uncontrolled clinical studies, laboratory analysis, animal testing, and epidemiological evidence. The following are only a few of the many examples of structure/function claims, and general well-being claims, that are based on such evidence.

A. "Vitamin B12 Supports the Nervous System and Energy Metabolism"

Vitamin B12 is required for, among other things, central nervous system function and energy metabolism.[26] These accepted roles of vitamin B12 in the body are based on a variety of different types of research. First, in 1926, an uncontrolled study of 45 patients with pernicious anemia revealed that a diet with liver and other meat reversed the condition.[27] Next, in 1948, laboratory testing isolated B12 as the substance responsible for the effect.[28] Further laboratory testing, including *in vitro* testing in human and rodent cell lines, revealed that B12 contributes to myelin formation and remyelination, functions crucial to maintain and regenerate the myelin sheaths that surround certain nerve axons.[29] Laboratory research also revealed the role of B12 in regulating mitochondrial enzymes crucial to energy metabolism.[30] This research – not dependent on randomized, controlled clinical testing – underlies claims like "Vitamin B12 Supports the Nervous System and Energy Metabolism."

("[A]ny complete ban on a claim would be approved only . . . when there was almost no qualitive evidence in support of the claim . . .").

[25] FDA, Letter of Enforcement Discretion, Consumption of Cranberry Products and Reduced Risk of Recurrent Urinary Tract Infection in Healthy Women, Dkt. No. FDA-2018-Q-0739 (July 21, 2020).

[26] NIH, Vitamin B12 Fact Sheet for Health Professionals (last updated Dec. 22, 2022), https://ods.od.nih.gov/factsheets/VitaminB12-HealthProfessional/; O'Leary, Vitamin B12 in health and disease, *Nutrients* (Mar. 2010), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3257642/.

[27] Takahashi-Iñiguez, Role of vitamin B12 on methylmalonyl-CoA mutase activity, *Journal of Zhejiang University-Science B* (June 2012), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3370288/.

[28] *Id.*

[29] Calderón-Ospina, B Vitamins in the nervous system, *CNS Neuroscience & Therapeutics* (Jan. 2020), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6930825/; Adamo, Nutritional factors and aging in demyelinating diseases, *Genes & Nutrition* (Jan. 2014), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3896619/#CR46.

[30] Depeint, Mitochondrial function and toxicity: Role of the B vitamin family on mitochondrial energy metabolism, *Chemico-Biological Interactions* (Oct. 2006), https://pubmed.ncbi.nlm.nih.gov/16765926/.

Vitamin B12 supplements carrying such claims are commonplace in the market. Such products and claims no doubt serve the public health, as Congress intended with DSHEA, by providing consumers nutrition information and a means to fill gaps in the diet.

Such products and claims are particularly important where a wide variety of groups are at risk of deficiency or inadequate intake of B12. For example, people over 50 normally require supplementation to obtain enough B12.[31] Vegans can only obtain B12 through fortification or supplementation, and vegetarians are also less likely to have adequate intake. Those with gastrointestinal disorders like celiac disease and Crohn's "may be unable to absorb enough vitamin B12 from food to maintain healthy body stores."[32] Inadequate intake of B12 can result in conditions including fatigue, neurological damage, and infertility.[33] Inadequate intake of B12 has also been associated with higher risk of cardiovascular disease, cognitive decline, and age related macular degeneration.[34]

B. "Magnesium Supports Muscle and Heart Function"

Magnesium is critical for many processes in the body, including muscle function and normal heart rhythm.[35] These accepted roles of magnesium are based on an wide body of evidence other than randomized, controlled clinical studies.[36] Magnesium was first described in blood plasma in 1920, then shown to be essential for life in rats six years later.[37] In 1934, researchers published the first report of clinical manifestations of magnesium deficiency in humans.[38] The totality of evidence on the health benefits of magnesium has continued to accumulate from research not limited to randomized, controlled clinical trials.

The body of research on magnesium and muscle and heart function includes, for instance, testing in the neural axons of giant squid, isolated frog and dog hearts, and isolated human muscle tissue, as well as deficiency studies in animals and human case studies.[39] This type of research now underlies claims like the following: "Magnesium supports muscle function and heart function."

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31 NIH, Vitamin B12 Fact Sheet for Consumers (last updated July 7, 2021), https://ods.od.nih.gov/factsheets/VitaminB12-Consumer/.

32 *Id*.

33 Vitamin B12 Fact Sheet for Health Professionals; O'Leary (2010).

34 *Id.*

35 NIH, Magnesium Fact Sheet for Consumers (last updated Mar. 22, 2021), https://ods.od.nih.gov/factsheets/Magnesium-Consumer/; NIH, Magnesium Fact Sheet for Health Professionals (last updated June 2, 2022), https://ods.od.nih.gov/factsheets/Magnesium-HealthProfessional/.

36 Magnesium Fact Sheet for Health Professionals.

37 Baaij, Magnesium in man: Implications for health and disease, *Physiological Reviews* (Jan. 2015), https://journals.physiology.org/doi/epdf/10.1152/physrev.00012.2014.

38 *Id.*

39 Magnesium Fact Sheet for Health Professionals; Iseri, Magnesium: Nature's physiologic calcium blocker, *American Heart Journal* (July 1984), https://www.sciencedirect.com/science/article/abs/pii/0002870384905726.

Magnesium products with such claims are also commonplace in the market, and again, no doubt serve the public health, as Congress intended with DSHEA. Such claims are particularly important where Americans meet their magnesium needs only with the addition of supplements to their diet.[40] An estimated 80-90 percent of magnesium is lost in the refining of grains and processing of foods that are prevalent in the American diet, contributing to lower intake.[41]

Groups at particular risk of magnesium inadequacy include older Americans, as well as those with celiac or Crohn's disease, type 2 diabetes, or alcohol dependency.[42] Adequate intake of magnesium has been associated with a lower risk of conditions like type 2 diabetes, and inadequate intake may be a cause of conditions like migraines and osteoporosis.[43]

C. Other Nutrient Examples

As with the benefits of vitamin B12 and magnesium, the necessity of many other nutrients, like vitamin A for eye health, iron for oxygen transport, vitamin C for immune function, and choline for liver function have been established through purely non-clinical research or a mixture of clinical studies of varied designs along with non-clinical research.[44] Such nutrient connections provide the basis for a wide variety of common claims for both multivitamins and single-ingredient supplements – from general well-being claims like "Promotes healthy growth and development" to structure/function claims like, "Supports the immune system" and "Muscle health."

Such claims are particularly important where the 2015-2020 Dietary Guidelines for Americans reported that many Americans under-consume at least nine essential nutrients – potassium, dietary fiber,

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[40] Magnesium Fact Sheet for Consumers ("The diets of many people in the United States provide less than the recommended amounts of magnesium. However, "[w]hen the amount of magnesium people get from food and dietary supplements is combined . . . total intakes of magnesium are generally above recommended amounts.").

[41] *Id.*

[42] Magnesium Fact Sheet for Health Professionals.

[43] *Id.*

[44] Tanumihardjo, Biomarkers of nutrition for development (BOND)—Vitamin A review, *The Journal of Nutrition* (Aug. 2016), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4997277/pdf/jn229708.pdf (describing non-clinical evidence establishing the need for vitamin A for eye health); Saha, Hemoglobin expression in nonerythroid cells: Novel or ubiquitous? *International Journal of Inflammation* (Nov. 2014), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4241286/pdf/IJI2014-803237.pdf; Andrews, Forging a field: The golden age of iron biology, *Blood* (July 2008), https://ashpublications.org/blood/article/112/2/219/24241/Forging-a-field-the-golden-age-of-iron-biology; Sheftel, The long history of iron in the universe and in health and disease, *Biochimica et Biophysica Acta* (Mar. 2012), https://www.sciencedirect.com/science/article/abs/pii/S0304416511001851?via%3Dihub; Carr, Vitamin C and immune function, *Nutrients* (Nov. 2017), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5707683/ (reviewing research on vitamin C and immune function); Zeisel, Choline: An essential nutrient for public health, *Nutrition Reviews* (Nov. 2009), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2782876/ (reviewing research on choline).

choline, magnesium, calcium, and vitamins A, C, D, and E.[45] While the Dietary Guidelines for Americans urge dietary shifts to nutrient dense foods, they aptly recognize that dietary supplements can "provid[e] one or more nutrients that otherwise may be consumed in less than recommended amounts or that are of particular concern for specific population groups."[46]

III. CRN Is Concerned About Statements in the New Guidance that Attempt to Remove the Legally Required Flexibility in CARSE and Impose a Rigid, Inaccurate Substantiation Standard on All Product Health Information

CRN appreciates that, like the 1998 FTC guidance on dietary supplement advertising, the FTC's new Health Products Compliance Guidance (Guidance) recognizes that what "constitutes a reasonable basis depends greatly on what claims are made, how they are presented in the context of the entire ad, and how they are qualified."[47] CRN also agrees that dietary supplement general well-being and structure/function claims normally require "competent and reliable scientific evidence."[48] Finally, CRN appreciates the Guidance acknowledging that evaluation of claim substantiation requires consideration of the *Pfizer* factors – including the "type of product," the "benefits of a truthful claim," the "cost or feasibility of developing substantiation for the claim," the "consequences of a false claim," and the "amount of substantiation that experts in the field believe is reasonable."[49]

Importantly, this type of balancing of consequences and risks to consumers while ensuring access to safe and beneficial products and information was exactly what Congress did when enacting DSHEA. As discussed above, Congress found that public health benefits from regulation that does not unnecessarily stifle innovation, access, and the development of health information. On the other hand, a more rigid and specific standard has been reserved for drug products – products that are intended, not just to support or maintain health, but to have a direct effect on disease.

CRN is, however, extremely concerned that, despite the foregoing, the Guidance also includes statements such as:

- "As a general matter, substantiation of health-related benefits will need to be in the form of randomized, controlled human clinical testing to meet the competent and reliable scientific [evidence] standard"; and
- "Randomized, controlled human clinical trials (RCTs) . . . are generally the type of substantiation that experts would require for health benefit claims."[50]

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45 Dietary Guidelines for Americans 2015-2020, at 60 https://health.gov/sites/default/files/2019-09/2015-2020_Dietary_Guidelines.pdf.

46 *Id.* at 11.

47 FTC, Health Prod. Compliance Guidance, at 11 (2022); *see also* Dietary Supplements: An Advertising Guide for Industry, at 8.

48 Guidance, at 3.

49 *Id.* at 11-12.

50 *Id.* at 12-13 (internal references omitted).

In addition to such broad statements, the Guidance further provides that, among other things, such RCTs should not only be randomized and controlled, but also "blinded to the fullest extent possible," yield statistically significant results between-group, avoid any post-hoc analysis, yield clinically meaningful results, have a "clear and detailed protocol" that has been reviewed by an institutional review board, be registered in a public database, include clear inclusion and exclusion criteria, use intent to treat analysis, be of "sufficient duration," have a formal manuscript, and be subject to "rigorous, unbiased peer review."[51]

A. Any Broad Requirement for RCTs for Dietary Supplements and Food Is Contrary to Congress's Purpose

The Guidance makes the above statements suggesting bright-line RCT use across what appears to be a broad array of products and claims, without attempting to distinguish between various statutorily defined product categories, claims, and standards discussed in Section I. The terms "health products" and "health benefit claim" are used throughout the guidance, but are never defined, and have never been used or defined in any statutory regime created by Congress. These vague and problematic terms would seem to cover any product making any conceivable claim related to health, regardless of the nature of the product or the significant differences in the way these products are regulated. Likewise, as discussed in greater detail below in Section VI, examples in the Guidance repeatedly suggest that dietary supplement marketers might lawfully use disease claims as long as such claims are supported by randomized, clinical testing and otherwise non-misleading – ignoring that these types of claims require FDA health claim authorization or drug approval. Creating further confusion, when the Guidance uses the term "health claim," it never acknowledges or clarifies that this is a term of art referring to specific type of FDA-authorized disease claim. Recognizing how various products are regulated by FDA and tailoring the new Guidance to specific product categories would be more useful to advertisers and help ensure that advertisers recognize FDCA obligations.

B. The RCT Standard in the New Guidance Inexplicably Exceeds FDA Standards for Drug Approval

Any "general" requirement that claims for dietary supplements and food are supported by RCTs is fundamentally at odds with the product category and claims regimes Congress created. As discussed in Section I, Congress specifically exempted dietary supplements from drug approval and avoided imposing any clinical trial requirements for dietary supplement or food claims. But, the supposed requirement for RCTs delineated in the new Guidance in fact even exceeds FDA standards for drug approval, which while still rigid and specific, build in flexibility to accommodate the fact-specific nature of health research.

As described in Section I, the FDA standard for new drug approval is the more rigid "substantial evidence" standard defined in the FDCA. The FDA's guidance on the "substantial evidence" standard explains that "[a]lthough randomized double-blinded, concurrently controlled superiority trials are usually regarded as the most rigorous design," "five types of controls" are also considered as alternatives: "placebo concurrent control, dose-comparison concurrent control, no treatment concurrent control, active treatment concurrent control, and historical control (a type of external

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[51] *Id*. at 16-18.

control)."[52] The guidance acknowledges potential weaknesses of these alternative designs, such as studies with no treatment concurrent control necessarily being unblinded and studies with external controls necessarily lacking randomization.[53] The guidance explains, though, that it "include[s] trial designs" that "may be more difficult to interpret" due to weaker designs because "different trial designs (including choice of control) may be appropriate in different disease settings."[54]

If the *Pfizer* factors are to have any meaning at all, it cannot be that claims for a drug – a potentially dangerous and often incredibly expensive product intended to directly affect disease – are subject to a lesser substantiation standard than structure/function and general well-being for dietary supplements and food. If the product categories and claims regimes Congress created for dietary supplements and food are to have any meaning at all, it cannot be that claims for a drug are subject to a lesser substantiation standard than structure/function and general well-being claims for dietary supplements and food. Had Congress intended this more specific and rigid standard to be used for supplement and food claims, it would have legislated accordingly. But, it never has.

Notably, the FTC appears to recognize this distinction in its April 2023 Notice of Penalty Offenses Concerning Substantiation of Product Claims, where the Commission cited to a more flexible CARSE standard for general health benefit claims and a heightened clinical trial standard for claims that "a product is effective in the cure, mitigation, or treatment of any serious disease."[55] The new FTC staff Guidance should reflect the interpretation of the flexibility in the substantiation standard recognized by the FTC Commissioners in the Notice of Penalty Offenses Concerning Substantiation of Product Claims.

C. The RCT Standard in the New Guidance Discourages the Dissemination of Truthful Nutrition Information

With its sweeping statements as to RCTs, the new Guidance leaves open whether the FTC believes that general well-being and structure/function claims like those discussed in Section II require RCTs.

In a void of guidance other than the FTC's repeated suggestions that RCTs are likely required, dietary supplement and food marketers are left to risk being the target of FTC enforcement or else to self-censor, to the detriment of their businesses and the consuming public. There can be no question that claims like "Magnesium for muscle function" or "Vitamin A for eye health" are truthful and adequately supported by evidence other than RCTs.

It is no solution to say that companies should commission RCTs for such claims out of an abundance of caution. First, randomized, controlled clinical studies, where healthy participants would be provided a

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[52] FDA, Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products, at 5 (Dec. 2019), https://www.fda.gov/media/133660/download.

[53] *Id*.

[54] *Id*.

[55] FTC, Notice of Penalty Offenses Concerning Substantiation of Product Claims (undated), https://www.ftc.gov/system/files/ftc_gov/pdf/Substantiaton-NPO.pdf. CRN is not commenting on the validity of these notices as a tool to collect civil penalties. CRN shares concerns raised by other trade associations and FTC-expert attorneys about their validity. Rather, CRN cites to them here as evidence that the FTC still does recognize a flexible standard, which contradicts the FTC staff's updated substantiation guidance.

nutrient like magnesium or B12, or a placebo, could at most show the effects of deficiency. Such clinical testing could *not* lead to the many discoveries that have been made about the precise functions like the role of B12 in myelin formation and remyelination. RCTs, moreover, involving providing participants with a placebo instead of an essential nutrient, like magnesium or B12, would be unethical at this point given the established necessity of such nutrients to human health. Finally, the cost of RCTs is extremely high and would be difficult, if not impossible, to recoup for relatively low-cost products that lack similar patent protections (and accompanying monopoly pricing) as drugs.

Particularly where any broad RCT requirement lacks a basis in the FTC Act or case law, conflicts with the claims regimes created by Congress, and fails to align with the commercial speech doctrine,[56] CRN urges the FTC to simply clarify that its Guidance describes its view of the ideal RCT. But, there is no bright-line requirement that dietary supplement or food marketers conduct or possess such evidence for structure/function or general well-being claims.

D. Any Broad Requirement for RCTs for Dietary Supplement and Food Claims Is Likely to Fail as a Legal Matter

In any event, apart from failing to align with existing statutory frameworks for claims, any bright-line requirement for RCTs is likely to fail as a legal matter. "[W]hat constitutes competent and reliable scientific evidence . . . is a question of fact for expert interpretation."[57] Therefore, as a matter of law, the FTC cannot impose a one size fits all standard, requiring particular types of clinical studies or even requiring clinical studies at all.

As support for its broad conclusions that RCTs – the highest level of medical research – are generally required for claims about "health benefit[s]" or "health-related benefits," the FTC cites a total of eight cases.[58] However, rather than support a broad legal requirement for RCTs, those cases simply show the CARSE factual analysis at work.

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[56] *See, e.g.*, *FTC v. Nat'l Urological Group, Inc.*, 785 F.3d 477, 481-482 (11th Cir. 2015) (rejecting a district court finding that "some form of clinical trial must have been conducted" in order to provide adequate CARSE for health-related claims); *FTC v. QT, Inc*., 512 F.3d 858, 862 (7th Cir. 2008) ("Nothing in the Federal Trade Commission Act, the foundation of this litigation, requires placebo-controlled, double-blind studies."); *Cooksey v. Futrell*, 721 F.3d 226 (4th Cir. 2013) (threats of enforcement by North Carolina Board of Dietetics and Nutrition chilled dietary advice, including both commercial and non-commercial speech, sufficient to show injury in fact).

[57] *FTC v. Quincy Bioscience Holding Co., Inc*., No. 17 CIV. 124 (LLS), 2022 WL 17905783, at *4 (S.D.N.Y. Dec. 19, 2022) (citing *FTC v. Alcoholism Cure Corp*., No. 3:10-cv-266-J-34JBT, 2011 WL 13137951, at *27 (M.D. Fla. Sept. 16, 2011), aff'd sub nom. *FTC v. Krotzer*, No. 12-14039-AA, 2013 WL 7860383 (11th Cir. May 3, 2013) (quoting *Nat'l Urological Grp*., Inc., 645 F. Supp. 2d at 1190, aff'd, 356 F. App'x 358 (11th Cir. 2009)).

[58] *See* Guidance, at 37-38 n. 31, 33 (citing *FTC v. Roca Labs, Inc*., 345 F. Supp. 3d 1375 (M.D. Fla. 2018); *FTC v. Nat'l Urological Grp., Inc*., No. 1:04-CV-3294-CAP, 2017 WL 6759868 (N.D. Ga. Oct. 10, 2017), aff'd, 786 F. App'x 947 (11th Cir. 2019); *POM Wonderful, LLC v. FTC*, 777 F.3d 478 (D.C. Cir. 2015); *COORGA Nutraceuticals Corp*., 201 F. Supp. 3d 1300 (D. Wy. 2016); *Nat'l Urological Grp., Inc*., 645 F. Supp. 2d 1167, aff'd, 356 F. App'x 358; *FTC v. Direct Mktg. Concepts, Inc*., 624 F. 3d 1 (1st Cir. 2010); *Removatron Int'l Corp*., 111 F.T.C. 206 (1988) aff'd, 884 F.2d 1489, 1498 (1st Cir. 1989); *Thompson Med. Co., Inc*., 104 F.T.C. 648 (1984)).

Four of the eight cases involved claims to treat diseases such as cancer and erectile dysfunction.[59] One involved outlandish weight loss claims, like "Benzedrine simply blows fat away," "Fat Assassin," and "WARNING: Extremely potent diet aid! Do not consume unless rapid fat and weight loss are your desired result."[60] The final three cases involved, respectively, claims that a drink could substitute for gastric bypass surgery, and strong cause and effect claims to permanently remove unwanted hair, and to prevent or permanently reverse gray hair.[61] In each case, the court found the claims at issue to be particularly strong. For instance, the court in one of the disease cases observed that the defendants "shill[ed] purported panaceas," "claimed [to] cure[] literally every disease, from cancer to Parkinson's to obesity."[62] After reviewing the claims, the courts next considered expert testimony on level of support necessary and assessed, based on that testimony, the level of support the defendants possessed. The courts, finally, found that claims lacked adequate support. Such analysis is the correct factual analysis that must be undertaken under the CARSE standard, but does not support the position that RCTs are always required. It demonstrates the opposite – that the type of claim being made dictates the level of support.

This is evident where the exact same factual analysis has also been at play in the several cases in recent years where the FTC failed to convince courts that dietary supplement structure/function claims require the high level of RCT support the agency is now advancing in its new Guidance.[63] For instance, *United States v. Bayer Corp.* involved claims that a probiotic supplement "helps defend against occasional constipation, diarrhea, gas, and bloating."[64] Bayer relied on clinical studies employing various designs to test one or more probiotic strains in various populations (*e.g.*, adults with irritable bowel syndrome).[65] Two experts offered by Bayer concluded that the evidence was adequate.[66] The FTC's scientific expert opined that the evidence was inadequate given that no single study constituted a clinical study that among other attributes was on the full product formulation, was "randomized, placebo-controlled, and double-blind," and "used validated methods and appropriate statistical methods to assess outcomes."[67] The court sided with Bayer, finding that testimony by the FTC's expert "conflicts with the longstanding understanding" of the competent and reliable scientific evidence standard.[68]

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59 *POM Wonderful, LLC*, 777 F.3d at 484; *Direct Mktg. Concepts, Inc*., 624 F. 3d 1; *Thompson Med. Co., Inc*., 104 F.T.C. 648; *Nat'l Urological Grp*., Inc., 645 F. Supp. 2d at 1190, aff'd, 356 F. App'x 358 (involving erectile dysfunction claims and disease claims to treat obesity).

60 *Nat'l Urological Grp., Inc*., No. 1:04-CV-3294-CAP, 2017 WL 6759868, at *6.

61 *Roca Labs, Inc*., 345 F. Supp. 3d at 1381; *COORGA Nutraceuticals Corp*., 201 F. Supp. 3d at 1305; *Removatron Int'l Corp*., 884 F.2d at 1491.

62 *Direct Mktg. Concepts, Inc*., 624 F. 3d at 1.

63 *See, e.g.*, *United States v. Bayer Corp*., No. CV 07-01(JLL), 2015 WL 5822595, at *8-9 (D.N.J. Sept. 24, 2015); *FTC v. Garden of Life, Inc*., 845 F. Supp. 2d 1328 (S.D. Fla. 2012), aff'd 516 F. App'x 852 (11th Cir. 2013); *Basic Research, LLC v. FTC*, No. 2:09-cv-0779, 2014 WL 12596497, at *35-36 (D. Utah Nov. 25, 2014).

64 No. CV 07-01(JLL), 2015 WL 5822595, at *5.

65 *Id.* at *7-9.

66 *Id.* at *10-11.

67 *Id.* at *4.

68 *Id.* at *16.

As another example, *FTC v. Garden of Life, Inc*. involved focus and mood claims for an omega-3 dietary supplement intended for children.[69] Garden of Life relied on several studies, which its expert found adequate.[70] However, the FTC's expert testified that the studies were "insufficiently rigorous" or only in children under age two.[71] The court found in favor of Garden of Life. It reasoned that holding Garden of Life liable "solely because another well-respected expert defines 'brain development' differently or disagrees with certain aspects of a study's trial design would require this Court to read additional requirements" into the applicable competent and reliable scientific evidence standard.[72]

The FTC can no more change court precedent through guidance than it can, through guidance, convert CARSE from a factual standard to a legal requirement for RCTs. Whether and what type of clinical testing might be required for a claim will always depend on "variable factors [such] as the nature of the claim being made, the nature of the product being studied, how dramatic or subtle the studied effect is, and the context of the surrounding scientific literature."[73]

IV. CRN Is Concerned that the New Guidance Suggests that Full Product Testing Is Required

While CRN appreciates the apparent acknowledgments in the Guidance that testing on individual ingredients can be sufficient to substantiate structure/function claims, it is nevertheless concerned that the Guidance attempts to suggest that this is the exception rather than the rule – and a rare exception at that. In addressing the importance of a study's relevance to an advertised product and the claims made for it, the Guidance makes the entirely reasonable suggestion that an advertiser consider whether "the ingredient or combination of ingredients in the advertised product [is] the same as what was used in the study."[74]

Yet, in the footnote to this sentence, the Guidance cites only two federal district court decisions and appends parentheticals that, particularly as to the first citation, suggest that testing of a product's full combination of ingredients might always be necessary:

- "*FTC v. Wellness Support Network, Inc*., No. 3:10-cv-04879 (N.D. Cal. Feb. 19, 2014) (accepting expert requirement that RCTs for diabetes supplement should be on the same dosage and formulation rather than on individual ingredients because 'there may be interactions between the ingredients that affect their physiological actions')"; and
- "*FTC v. Nat'l Urological Grp., Inc*., 645 F. Supp. 2d [1167] at 1202 [(N.D. Ga. 2008)] (accepting undisputed expert testimony that a study on a different dose or a different combination of active ingredients would not be sufficient to substantiate an efficacy claim)."[75]

What these case citations fail to acknowledge clearly is that the findings as to product testing were, in no uncertain terms, because the claims at issue were disease claims in the first case cited, and in the

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69 516 F. App'x at 856; *see also* 845 F. Supp. 2d at 1334-1335.

70 516 F. App'x at 856.

71 *Id.* at 852; *see also* 845 F. Supp. 2d at 1335.

72 845 F. Supp. 2d at 1334, aff'd 516 F. App'x at 856-857.

73 FTC Resp. to Rulemaking Petition by Whitaker, *et al*., Project No. P004501, at 6.

74 Guidance, at 23.

75 *Id.*, at 23 n. 45.

second case, because there was simply no other expert to counter the FTC's. Specifically, in the case involving the diabetes supplement, the FTC's expert opined that full product testing would be required, not only because of potential ingredient interaction, but moreover "because [the claims were] disease-specific treatment or prevention claims."[76] In the other case, the court explicitly stated that it followed the opinions of the FTC experts because the defendant offered no expert testimony, so that there was "no issue of fact regarding the requisite levels of substantiation."[77] CRN suggests that the Guidance ought to acknowledge clearly these rationales for requiring full product testing in two discrete cases, and moreover acknowledge that many other courts have accepted ingredient testing.

Apart from the two cited cases, federal courts have repeatedly approved substantiation based on testing of individual product ingredients.[78] In one such case, the FTC's own expert stated that an "acceptable study" for substantiation purposes would be one in which participants consume "one or more of the active ingredients" in the product.[79]

Further, CRN notes that the "essentially equivalent product" standard continues to be valid and repeatedly reinforced by FTC orders. There is little difficulty in locating numerous FTC orders issued even since the publication of the Guidance that state that an "essentially equivalent product" may contain ingredients in addition to those tested "if reliable scientific evidence generally accepted by experts in the field indicates that the amount and combination of additional ingredients is unlikely to impede or inhibit the effectiveness of the ingredients in the Essentially Equivalent Product."[80]

This standard is therefore not a new one for the agency; it is one the agency has repeatedly applied in a variety of contexts. CRN believes that the agency would, therefore, do well to clarify the confusion created by the Guidance's selective case citations on the issue of product versus ingredient testing.

V. CRN Is Concerned About the Expert Standard in the New Guidance

For decades, the FTC has defined CARSE as "tests, analyses, research, studies or other evidence based on the *expertise of professionals in the relevant area*, that have been conducted and evaluated in an objective manner by persons qualified to do so, using procedures generally accepted in the profession to yield accurate and reliable results."[81] The new Guidance purports to redefine CARSE as "tests, analyses, research, or studies that (1) have been conducted and evaluated in an objective manner by experts in the *relevant disease, condition, or function to which the representation relates*, and (2) are generally accepted in the profession to yield accurate and reliable results." This new definition of who might be an

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[76] *Wellness Support Network*, No. 3:10-cv-04879, 2014 WL 644749, at *16.

[77] *Nat'l Urological Grp.,* 645 F. Supp. 2d at 1202.

[78] *See, e.g., Bayer Corp.*, No. 07-cv-01, 2015 WL 5822595, at *16; *Garden of Life, Inc.*, 845 F. Supp. 2d at 1338.

[79] *Basic Research*, No. 2:09-CV-0779 CW, 2014 WL 12596497, at *6, 12.

[80] *See, e.g., United States v. Connors*, No. 23-cv-475 (M.D. Fla. July 26, 2023); *FTC v. Rejuvica LLC*, No. 23-cv1286, 2023 WL 4673263 (C.D. Cal. July 20, 2023); *United States v. Akoury*, No. 23-cv-26 (E.D. Tenn. Mar. 21, 2023); *FTC v. Zycal Bioceuticals*, No. 20-cv-10249 (D. Mass. Feb. 7, 2023).

[81] *See, e.g.*, Dietary Supplements: An Advertising Guide for Industry, at 9; Comments in the Matter of Proposed Rule: Regulations on Statements Made for Dietary Supplements Concerning the Effect of the Product on the Structure or Function of the Body, FDA Dkt. No. 98N-0044, at 2; FTC Resp. to Rulemaking Petition by Whitaker, *et al*., Project No. P004501, at 4.

appropriate expert lacks any statutory or other legal basis and is unduly restrictive, suggesting that a professional like a nutrition researcher, nutritionist, or pharmacologist might not be an appropriate expert to assess substantiation for dietary supplement claims.

As noted above, the *Garden of Life* case involved "advertising claims that [a dietary supplement] benefitted children's cognitive development, mental focus, and mood and behavior."[82] The FTC argued that a clinical pharmacologist on the defense side failed to be an expert "in the relevant area" because he was not an expert specifically in the "field of children's cognitive and behavioral development and thus was unqualified to evaluate the relevant studies."[83] The Eleventh Circuit squarely rejected that argument, finding that the clinical pharmacologist held a "Ph.D. in Pharmacology" and had "twenty years of experience in evaluating scientific evidence to substantiate advertising and label claims."[84]

The FTC cannot undo *Garden of Life* by writing into guidance its failed argument as to the appropriate expert to interpret the CARSE standard. CRN requests that the FTC clarify that, in fact, there is no rigid requirement that scientific experts evaluating claim substantiation must be expert in the "relevant disease, condition, or function to which the representation relates."

VI. Examples in the Guidance Risk Suggesting Dietary Supplements Can Be Promoted with Unapproved Disease Claims

In addition to its concerns as to substantiation standards, CRN is also concerned that the FTC's new Guidance fails to align with the claims regimes Congress created for dietary supplements and food, versus drugs. Specifically, examples provided in the Guidance repeatedly suggest that dietary supplement marketers might lawfully use disease claims as long as such claims are simply substantiated and otherwise non-misleading, ignoring that these types of claims are prohibited by the FDCA without FDA health claim authorization or drug approval. The following is a summary.

- Example 9 suggests that, as long as nausea is disclosed as a potential side effect, a marketer could promote its dietary supplement as a "natural pain remedy," regardless of whether pain is from an injury or disease versus a non-disease cause like exercise.
- Example 24 suggests that a marketer could promote the "anti-clotting effect" of its dietary supplement as long as the claim is adequately substantiated.
- Example 26 suggests that a marketer could promote its dietary supplement for "symptoms of osteoarthritis" as long as the claim is adequately substantiated.
- Examples 28 and 29 suggest that a marketer could promote its dietary supplement for "erectile dysfunction" as long as the claim is adequately substantiated.
- Examples 36 suggests that a marketer could promote its dietary supplement for "symptoms of Crohn's disease" as long as the claim is adequately substantiated.
- Examples 40 suggests that, with adequate substantiation, a marketer could promote its dietary supplement as a "cure [for] acid reflux," regardless of whether the persistence or severity might classify the condition as a disease.

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82 516 F. App'x at 856.

83 *Id.* at 857.

84 *Id*.

- Example 47 suggests that a marketer could promote its dietary supplement for "treat[ing] diabetes" as long as the claim is adequately substantiated.
- Examples 50 and 51 suggest that a marketer could promote its dietary supplement as a "Miracle Cancer Cure" as long as the claim is adequately substantiated.

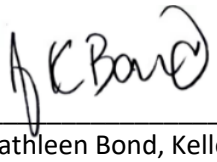
CRN would appreciate the FTC rescinding and avoiding such examples, or clarifying that, under the FDCA, such claims would cause a product to be misbranded as an unapproved new drug, regardless of the level of substantiation or any disclosures. The examples, as currently written, create undue confusion as to what claims are allowed for dietary supplements.

Conclusion

We strongly encourage FTC to review the new Guidance in light of all relevant legal factors and work with stakeholders, including FDA, to make necessary edits. As described above, it is of particular importance to CRN that the FTC clarify that:

- there is no bright-line requirement that a company possess randomized, controlled clinical studies before making "health benefit" claims for dietary supplements or food;
- there is no requirement for full product testing versus testing of certain ingredients;
- professionals like nutrition researchers, nutritionists, and pharmacologists can be suitable scientific experts to assess substantiation for dietary supplement and food claims; and
- dietary supplements and foods are prohibited from making claims to treat or prevent disease without authorization from the FDA.

Respectfully submitted,



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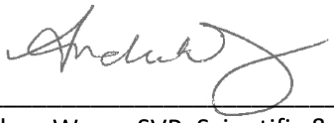

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